Amendments to the Specification:

Please replace the paragraph beginning at page 1, line 4, with the following rewritten paragraph.

The present application is a ~~Continuation application of co-pending~~ continuation of U.S. Patent Appln. ~~Ser.~~ No. 08/912,951, filed August 14, 1997, now U.S. Patent No. 6,475,789, which is a ~~Continuation In Part~~ continuation-in-part ~~application~~ of U.S. Patent Appln. ~~Ser.~~ No. 08/854,050, filed May 9, 1997, now U.S. Patent No. 6,261,836, which is a ~~Continuation In Part application~~ continuation-in-part of U.S. Patent Appln. ~~Ser.~~ No. 08/851,843, filed May 6, 1997, now U.S. Patent No. 6,093,809, which is a ~~Continuation In Part application~~ continuation-in-part of U.S. Patent Appln. ~~Ser.~~ No. 08/846,017, filed April 25, 1997, now abandoned, which is a ~~Continuation in Part application~~ continuation-in-part of U.S. ~~Paten Appln. Ser.~~ Patent Appln. No. 08/844,419, filed April 18, 1997, now abandoned~~, which is a Continuation in Part application of U.S. Patent Appln. Ser. No. 08/724,643, filed on October 1, 1996, now abandoned~~. Each of the aforementioned applications is explicitly incorporated herein by reference in its entirety and for all purposes.

Please replace the paragraph beginning at page 8, line 32, with the following rewritten paragraph.

~~Figure 10 shows~~ Figures 10A and 10B show coexpression *in vitro* of the hTRT and hTR to produce catalytically active human telomerase.

Please replace the paragraph beginning at page 9, line 8, with the following rewritten paragraph.

~~Figure 13 (SEQ. ID. NO: 109) shows~~ Figures 13A and 13B (SEQ ID NO: 109) show the sequence of the DNA encoding the *Euplotes* 123 kDa telomerase protein subunit.

Please replace the paragraph beginning at page 9, line 12, with the following rewritten paragraph.

~~Figure 15 (SEQ. ID NOS: 111-112) shows~~ Figures 15A-15F (SEQ ID NOS: 111-112) show the DNA and amino acid sequences of the *S. pombe* telomerase catalytic subunit.

Please replace the paragraph beginning at page 9, line 20, with the following rewritten paragraph.

~~Figure 20 shows~~ Figures 20A-20E show the sequence of a nucleic acid encoding a Δ182 variant polypeptide (SEQ ID NO: 4).

Please replace the paragraph beginning at page 9, line 22, with the following rewritten paragraph.

~~Figure 21 shows~~ Figures 21A-21E show the sequence from an hTRT genomic clone (SEQ ID NO: 6).

Please replace the paragraph beginning at page 10, line 28, with the following rewritten paragraph.

As described in detail in the above-referenced priority documents, TRT was initially characterized following purification of telomerase from the ciliate *Euplotes aediculatus*. Extensive purification of *E. aediculatus* telomerase, using RNA-affinity chromatography and other methods, yielded the protein "p123". Surprisingly, p123 is unrelated to proteins previously believed to constitute the protein subunits of the telomerase holoenzyme (i.e., the p80 and p95 proteins of *Tetrahymena thermophila*). Analysis of the p123 DNA and protein sequences (Genbank Accession No. U95964; ~~**Figures 13 and 14**~~ **Figures 13A, 13B and 14**) revealed reverse transcriptase (RT) motifs consistent with the role of p123 as the catalytic subunit of telomerase (see, e.g., **Figure 1**). Moreover, p123 is related to a *S. cerevisiae* (yeast) protein, Est2p, which was known to play a role in maintenance of telomeres in *S. cerevisiae* (Genbank

Accession No. S5396), but prior to the present invention was not recognized as encoding a telomerase catalytic subunit protein (see, e.g., Lendvay et al., 1996, *Genetics*, 144:1399).

Please replace the paragraph beginning at page 19, line 22, with the following rewritten paragraph.

The present invention provides isolated and recombinant nucleic acids having a sequence of a polynucleotide encoding a telomerase catalytic subunit protein (TRT), such as a recombinant TRT gene from *Euplotes, Tetrahymena, S. pombe* or humans. Exemplary polynucleotides are provided in ~~**Figure 13**~~ **Figures 13A and 13B** (*Euplotes*); ~~**Figure 15**~~ **Figures 15A-15F** (*S. pombe*) and **Figure 16** (human, GenBank Accession No. AF015950). The present invention provides sense and anti-sense polynucleotides having a TRT gene sequence, including probes, primers, TRT-protein-encoding polynucleotides, and the like.

Please replace the paragraph beginning at page 20, line 1, with the following rewritten paragraph.

In one aspect, the invention provides a polynucleotide having a sequence or subsequence of a human TRT gene or RNA. In one embodiment, the polynucleotide of the invention has a sequence of **SEQ ID NO: 1,** or a subsequence thereof. In another embodiment, the polynucleotide has a sequence of **SEQ ID NO: 3 (Figure 18), SEQ ID NO: 4** ~~**(Figure 20)**~~ **(Figures 20A-20E),** or subsequences thereof. The invention also provides polynucleotides with substantial sequence identity to the hTRT nucleic acid sequences disclosed herein, e.g., **SEQ ID NO: 1** and any others disclosed (e.g., **SEQ ID NOS: 4, 6** ~~**[Figure 21]**~~ **[Figures 21A-21E],** and **7 [Figure 22]**). Thus, the invention provides naturally occurring alleles of human TRT genes and variant polynucleotide sequences having one or more nucleotide deletions, insertions or substitutions relative to an hTRT nucleic acid sequence disclosed herein. As described *infra*, variant nucleic acids may be produced using the recombinant or synthetic methods described below or by other means.

Please replace the paragraph beginning at page 37, line 27, with the following rewritten paragraph.

The invention also provides other naturally ~~occuring~~ occurring hTRT species or nonnaturally occuring variants, such as proteins having the sequence of, or substantial similarity to **SEQ ID NO: 5 [~~[Figure 20~~ Figures 20A-20E], SEQ ID NO: 10 ~~[Figure 20]~~ [Figure 19],** and fragments, variants, or derivatives thereof.

Please replace the paragraph beginning at page 37, line 31, with the following rewritten paragraph.

The invention provides still other hTRT species and variants. One example of an hTRT variant may result from ribosome frameshifting of mRNA encoded by the clone 712562 **(SEQ ID NO: 3 [Figure 18]) or** the pro90 variant hTRT shown in **SEQ ID NO: 4 ~~[Figure 20]~~ [Figures 20A-20E]** and so result in the synthesis of hTRT polypeptides containing all the TRT motifs (for a general example, see, e.g., Tsuchihashi et al., 1990, *Proc. Natl. Acad. Sci. USA* 87:2516; Craigengen et al., 1987, *Cell* 50:1; Weiss, 1990, *Cell* 62:117). Ribosome frameshifting can occur when specific mRNA sequences or secondary structures cause the ribosome to "stall" and jump one nucleotide forwards or back in the sequence. Thus, a ribosome frameshift event on the 712562 mRNA could cause the synthesis of an approximately 523 amino acid residue polypeptide. A ribosome frameshift event on the pro90 sequence could result in a protein with approximately 1071 residues. It will be appreciated that proteins resulting from ribosome frameshifting can also be expressed by synthetic or recombinant techniques provided by the invention.

Please replace the paragraph beginning at page 157, line 3, with the following rewritten paragraph.

This intron contains motifs characteristic of a topoisomerase II cleavage site and a NFκB binding site (see ~~Figure 21~~ Figures 21A-21E). These motifs are of interest, in part, because expression of topoisomerase II is up regulated in most tumors. It functions to relax DNA

by cutting and rewinding the DNA, thus increasing expression of particular genes. Inhibitors of topoisomerase II have been shown to work as anti-tumor agents. In the case of NFκB, this transcription factor may play a role in regulation of telomerase during terminal differentiation, NFκB may play a role in early repression of telomerase during development and so is another target for therapeutic intervention to regulate telomerase activity in cells.

Please replace the paragraph beginning at page 158, line 4, with the following rewritten paragraph.

Phage GΦ5 was mapped by restriction enzyme digestion and DNA sequencing. The resulting map is shown in **Figure 7**. The phage DNA was digested with *Nco*I and the fragments cloned into pBBS167. The resulting subclones were screened by PCR to identify those containing sequence corresponding to the 5' region of the hTRT cDNA. A subclone (pGRN140) containing a 9 kb *Nco*I fragment (with hTRT gene sequence and 4-5 kb of lambda vector sequence) was partially sequenced to determine the orientation of the insert. pGRN 140 was digested using *Sal*I to remove lambda vector sequences, resulting in pGRN144. pGRN144 was then sequenced. The sequence is provided in ~~**Seq. ID. NO: 6**~~ **SEQ ID NO: 6**. The 5' end of the hTRT mRNA corresponds to ~~base 2441~~ base 2258 of ~~**Seq. ID. NO: 6**~~ **SEQ ID NO: 6**. As indicated in **Figure 7**, two Alu sequence elements are located 1700 base pairs upstream of the hTRT cDNA 5' end and provide a likely upstream limit to the promoter region of hTRT. The sequence also reveals an intron positioned at base 4173 ~~**Seq. ID. NO: 6**~~ **SEQ ID NO: 6**, 3' to the intron described in **Example 3**, *supra.*

Please replace the paragraph beginning at page 158, line 30, with the following rewritten paragraph.

The human BAC clone (326 E 20) was obtained with a hybridization screen of a BAC human genomic library using an 1143 bp Sph1/Xmn1 fragment of **SEQ. ID. NO: 1** (bases 1552-2695) that encompasses the RT motif region. The clone is believed to include the 5' end. The hTRT genomic clones in this example are believed to encompass the entire hTRT gene.

Please replace the paragraph beginning at page 176, line 18, with the following rewritten paragraph.

The results of the reconstitution are shown in ~~Figure 10~~ **Figures 10A and 10B**. For each transcription/translation reaction there are 3 lanes: The first 2 lanes are duplicate assays and the third lane is a heat denatured (95°C, 5 min) sample to rule out PCR generated artifacts.

Please replace the paragraph beginning at page 176, line 22, with the following rewritten paragraph.

As shown in ~~Figure 10~~ **Figures 10A and 10B**, reticulocyte lysate alone has no detectable telomerase activity (lane 6). Similarly, no detectable activity is observed when either hTR alone (lane 1) or full length hTRT gene (lane 4) are added to the lysate. When both components are added (lane 2), telomerase activity is generated as demonstrated by the characteristic repeat ladder pattern. When the carboxy-terminal region of the hTRT gene is removed by digestion of the vector with *Nco*I ("truncated hTRT") telomerase activity is abolished (lane 3). Lane 5 shows that translation of the truncated hTRT also did not generate telomerase activity. Lane "R8" shows a positive control (TSR8 quantitation standard (SEQ ID NO: 329) (5'-ATTCCGTCGAGCAGAGTTAG[GGTTAG]7-3')).